

**Amendments to and Listing of the Claims:**

Please cancel claims 2-4, 7-9, 12 and 14, without prejudice or disclaimer. Please amend claims 1, 5, 6, 9, 10-17, without prejudice or disclaimer, and add a new claim 18, as set forth in the following listing of the claims, which will replace all prior versions, and listings, of claims in the application:

1. (Currently amended) A non-human transgenic animal selected from the group consisting of mice, rats, goats, pigs, sheep and cows, whose genome comprises:  
~~a mammary-specific expression cassette system comprising:~~

~~(a) a foreign DNA sequence encoding a mature polypeptide which contains full coding region or recombinant gene structure;~~

~~(b) a second DNA sequence which is a secretion signal sequence preceding and operably linked to upstream of (a), said signal sequence encoding a secretional peptide, whereby said mature polypeptide is secreted of high levels into milk by said mammary gland cells;~~

~~(c) a third DNA sequence which is polyadenylation signal sequence preceding and operably linked to downstream of (a), said polyadenylation signal sequence can be recognized by poly(A)-polymerase for polyadenylation tail editing, whereby said polyadenylation tail acts for stabilized the transgene mRNA molecules;~~

~~(d) a regulatory element of a gene encoding a milk protein of a mammary operably linked to the DNA sequences of (a), (b) and (c) above so as to form a hybrid gene which is expressible in the mammary gland of an adult lactating female of a transgenic animal whose genome comprises said hybrid gene; so that the mature polypeptide is secreted at detectable levels into milk of said mammal if said mammal is a lactating female.~~

(a) a nucleotide sequence encoding a B-domain deleted human clotting factor VIII (FVIII) polypeptide of SEQ ID NO: 15, wherein an innate N-terminal 19-amino acid signal peptide is replaced by a mammary gland-specific signal peptide sequence;

(b) a nucleotide sequence encoding a signal peptide comprising bovine  $\alpha$ -lactalbumin ( $\alpha$ -LA) of SEQ ID NO: 13 or bovine  $\alpha$ -S1 casein peptide of SEQ ID NO: 14, added to a N-terminal of the B-domain deleted human FVIII polypeptide of SEQ ID NO: 15; and

(c) an  $\alpha$ -LA promoter;

wherein the B-domain deleted human FVIII polypeptide is secreted in milk when the non-human transgenic animal is lactating.

2. – 4. (Canceled)

5. (Currently amended) The non-human transgenic animal ~~whose genome comprises a mammary specific expression cassette~~ according to claim 1, wherein the signal peptide is ~~an artificial synthetic sequence as SEQ ID NO: 1 which obtained from the  $\alpha$  bovine  $\alpha$ -lactalbumin~~  $\alpha$ -lactalbumin signal peptide and created encoded by a DNA sequence of SEQ ID NO: 1 with a restriction enzyme, HpaI, cloning site in downstream of the DNA sequence of SEQ ID NO: 1.

6. (Currently amended) The non-human transgenic animal ~~whose genome comprises a mammary specific expression cassette~~ according to claim 1, wherein the signal peptide is ~~an artificial synthetic sequence as SEQ ID NO: 2 which obtained from the  $\alpha$  bovine  $\alpha$ -S1 casein~~  $\alpha$ -S1 casein signal peptide and created encoded by a DNA sequence of SEQ ID NO: 2 with a restriction enzyme, HpaI, cloning site in downstream of the DNA sequence of SEQ ID NO: 2.

7. – 9. (Canceled)

10. (Currently amended) The non-human transgenic animal according to claim ~~3~~ 1, wherein ~~said the~~ nucleotide sequence encoding the B-domain deleted human FVIII polypeptide comprises a light chain (A3-C1-C2 domain) and a heavy chain (A1-A2 domain) and ~~wherein said the~~ light chain and heavy chain are operably linked by a junction.

11. (Currently amended) The non-human transgenic animal according to claim 9, wherein ~~said~~ the mammary gland-specific signal peptide sequences ~~are SEQ ID: NO: 13 and SEQ ID: NO: 14 for 19 residue of alpha lactalbumin and 15 residue of alpha-S1 casein signal peptides, respectively~~ comprises at least one of the bovine  $\alpha$ -lactalbumin of SEQ ID NO: 13 with 19 amino acid residues and the bovine  $\alpha$ -S1 casein peptide of SEQ ID NO: 14 with 15 amino-acid residues.

12. (Canceled)

13. (Currently amended) A method for ~~producing the~~ making the non-human transgenic animal of claim 1 comprising the steps of:

a.i. introducing into a mammalian an embryo at least one expression cassette system comprising a DNA sequence encoding a mature polypeptide which intact human FVIII or B domain-deleted human FVIII operatively linked to mammary gland-specific regulatory sequences of the non-human transgenic animal a transgene whose genome comprises (a) a nucleotide sequence encoding a B-domain deleted human clotting factor VIII (FVIII) polypeptide of SEQ ID NO: 15, wherein an innate N-terminal 19-amino acid signal peptide is replaced by a mammary gland-specific signal peptide sequence; (b) a nucleotide sequence encoding a signal peptide comprising bovine  $\alpha$ -lactalbumin ( $\alpha$ -LA) of SEQ ID NO: 13 or bovine  $\alpha$ -S1 casein peptide of SEQ ID NO: 14, added to a N-terminal of said B-domain deleted hFVIII polypeptide of SEQ ID NO: 15, and (c) an  $\alpha$ -LA promoter; and

b.ii. implanting the embryos-embryo into a female of the same species of the non-human transgenic animal;

iii. permitting the embryo to develop to full term; and

iv. identifying these the non-human transgenic animal producing mammals which produce in their milk that contains a detectable quantities of a mature polypeptide

~~which intact human FVIII or~~ quantity of the B domain-deleted human FVIII  
polypeptide.

14. (Canceled)

15. (Currently amended)     The method ~~for producing the transgenic animal~~ according to claim 13, wherein ~~a plurality of different~~ the transgene is presented in an expression cassettes ~~are~~ cassette that is introduced and these cassettes to the animal to express at least two different ~~mature polypeptides which intact human FVIII and~~ the B domain-deleted human FVIII polypeptide.

16. (Currently amended)     The method ~~of~~ according to claim 13, wherein the expression level of the human FVIII in the milk of ~~said the non-human transgenic animals can reach~~ animal is about 50 mg/L, and its the human FVIII has a clotting activity can reach about 13-fold higher than that of a clotting activity of human FVIII in normal human plasma.

17. (Currently amended)     The method ~~of~~ according to claim 13, wherein ~~the a~~ a purified human FVIII from the ~~transgenic milk can be applied for~~ of the non-human transgenic animal is applicable to a supplementary therapy used.

18. (New)     The non-human transgenic animal according to claim 1, wherein the  $\alpha$ -LA promoter is a 2.0-kb bovine  $\alpha$ -LA promoter.